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Evaluation of clinicopathological and prognostic significance of RDW in gastric cancer

RDW'nin mide kanserinde klinikopatolojik ve prognostik öneminin değerlendirilmesi

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ABSTRACT

Objective: We aimed to reveal possible relationships between pre-operative RDW values and clinicopathological features of gastric cancer (GC) and to evaluate its predictive impact on progression and prognosis of GC.

Material And Method: A total of 92 patients who underwent curative surgery were retrospectively included the study. GC patients were divided into two groups: high-RDW group (>14.5%, n=58) and low-RDW (<14.5%, n=34).

Results: The optimal pre-operative RDW cut-off value to predict mortality in GC patients was 14.5% (AUC=0.690, p=0.010). Increased tumor size and decreased albumin and hemoglobin values were found in the high-RDW group (p=0.036, 0.003 and <0.001, respectively). The 5-year overall survival (OS) rates were 17.6±5% in patients with high-RDW and 44.5±9% in the low-RDW group (p<0.001). Cox regression analysis showed perineural invasion, surgical margin positivity, N3 stage, leakage and high RDW were independent prognostic factors for mortality.

Conclusion: Our results indicate that RDW is associated with GC pathogenesis and tumor progression. Pre-operative RDW may be a non-invasive, easily accessible and reliable indicator to predict survival in patients with GC.

Keywords: Gastric cancer, red cell distribution width, RDW, prognosis, overall survival

ÖZ

Amaç: Preoperatif RDW değerleri ile mide kanseri (MK)'nin klinikopatolojik özellikleri arasındaki olası ilişkileri ortaya koymayı ve MK'nin progresyonu ve prognozu üzerindeki prediktif etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Küratif cerrahi uygulanan toplam 92 hasta retrospektif olarak çalışmaya dahil edildi. MK hastaları iki gruba ayrıldı: yüksek RDW grubu (>%14,5, n=58) ve düşük RDW (<%14,5, n=34).

Bulgular: MK hastalarında mortaliteyi öngörmek için optimal preoperatif RDW eşik değeri %14,5 idi (AUC=0,690, p=0,010). Yüksek RDW grubunda tümör boyutunda artış, albümin ve hemoglobin değerlerinde azalma saptandı (sırasıyla p=0,036, 0,003 ve <0,001). Yüksek RDW'li hastalarda 5 yıllık genel sağkalım (OS) oranları %17,6±%5 ve düşük RDW grubunda %44,5±%9 idi (p<0,001). Cox regresyon analizi perinöral invazyon, cerrahi sınır pozitifliği, N3 evresi, sızıntı ve yüksek RDW değerinin mortalite için bağımsız prognostik faktörler olduğunu gösterdi.

Sonuç: Sonuçlarımız, RDW'nin MK patogenezinde ve tümör progresyonunda rol oynadığını göstermektedir. Preoperatif RDW, MK'li hastalarda sağkalımı öngörmek için invazif olmayan, kolay erişilebilir ve güvenilir bir gösterge olabilir.

Anahtar Kelimeler: Mide kanseri, eritrosit dağılım genişliği, RDW, prognoz, genel sağkalım

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide, with almost one million new cases reported annually (1). Despite the global decline in incidence and mortality, as well as recent improvements in the management modalities of GC, treatment options still not promising enough and it remains the third leading cause of cancer-related death (2). Because GC is either asymptomatic or presents with non-specific signs and symptoms at early stages, most patients are usually diagnosed at an advanced stage. Most cases have regional or distant metastases at presentation, and overall 5-year survival is often less than 30% after surgical intervention with lymph node dissection and chemotherapy and radiotherapy administration(3). Therefore, identifying independent prognostic determinants may help predict and improve long-term outcomes in GC patients. Although several factors have been determined to stratify patient survival in different cohorts of GC patients, there is a still need for non-invasive, low-cost, and reliable predictors to establish prognostic models (4).

Accumulating evidence indicates that both systemic and local inflammatory responses play important roles in tumor progression by inducing invasion, migration, angiogenesis and metastasis, and are related with the prognosis of GC (5). Red blood cell distribution width (RDW) is a routine laboratory parameter and it is widely used to differentiate anemia in clinical settings (6). Previous studies also reported that elevated RDW value is related with systemic inflammation, malnutrition and cancer pathophysiology -including its development, progression and prognosis (7). Although, the prognostic value of the pre-operative RDW value for gastric cancer is still unclear.

The aim of this study was to evaluate the relationship between pre-operative RDW values and clinicopathological characteristics of GC and to investigate its prognostic significance in GC patients who underwent surgical treatment.

MATERIAL AND METHOD

The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 15.06.2021, Decision No: 03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a single center retrospective study and was carried out from January 2011 to January 2016 in General Surgery Department of Eskişehir Osmangazi University Hospital. A total of 92 patients (after exclusion) who underwent curative surgical intervention for histopathologically-diagnosed GC were included the study. Patients were randomly selected and only those with confirmed histopathological diagnosis, complete demographic, clinicopathological and follow-up data, and those in which complete blood counts had been perfromed before surgical intervention were included in the study. Patients with recurrent gastric cancer, synchronous or metachronous cancer, anemia, cirrhosis, clinical sign of infection, autoimmune diseases, hematological disorders, those who received neoadjuvant therapy or an emergency gastrectomy for bleeding or perforation, those using corticosteroids in the last 6 months, and patients with incomplete data were excluded from the study. A total of 20 patients had been excluded due to exclusion criteria. Since the study was designed as a retrospective evaluation, written informed consent from patients was waived.

Demographic features and clinicopathological characteristics, including type of surgical procedure, the size, histology, differentiation and primary location of tumor, Lauren classification, the number of lymph nodes and metastatic lymph nodes, perineural invasion, lymphovascular invasion, extracapsular invasion, surgical margin positivity, tumor stage, the length of hospitalization, the presence of leakage or infection, the recurrence status, and the final status were obtained from hospital records each patient. The tumor stage of patients was determined in accordance with the pathological classification criteria of the American Joint Committee on Cancer Staging / UICC-TNM for GC (8). Patients were divided into three main groups: diffuse, intestinal and mixed according to Lauren classification criteria (9). All patients were followed regularly with clinical and radiological evaluation every 3 to 6 months. Causes of death and recurrence status were assessed by reviewing medical records or by direct questioning of close relatives. The last follow-up evaluations were performed in September 2021. Overall survival (OS) was determined as the duration from the date of surgical procedures to the date of death or the last follow-up.

All analyses were performed on SPSS v21 (IBM, Armonk, NY, USA). Histograms and Q-Q plots were used to determine whether variables were normally distributed. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. The best cut-off for RDW to predict mortality was determined by using Receiver Operating Characteristics (ROC) curve analysis and the Youden J statistic. Continuous variables were analyzed with the independent samples t-test or the Mann-Whitney U test depending on normality of distribution. Categorical variables were analyzed with Pearson chi-square or Fisher's exact test. Survival times were calculated with the Kaplan-Meier

method. Between-group comparisons of survival times were performed with the Log rank test. Cox regression analysis (forward conditional method) was performed to determine significant prognostic factors. p<0.05 values were accepted as statistically significant results.

RESULTS

Demographic characteristics, laboratory results and clinicopathological data of GC patients are given in **Table 1**. The mean age of patients was 63.9±14.1 years and most of them were male (n:60, 65.22%). In the pathological evaluation, gastric adenocarcinoma was diagnosed in 60 (65.22%) patients, signet ring cell adenocarcinoma in 30 (32.61%) patients, and mucinous adenocarcinoma in 2 (2.17%) patients. Surgical intervention was applied to 66 (71.74%) patients as total gastrectomy, 25 (27.17%) patients as subtotal gastrectomy and 1 (1.09%) patient underwent laparoscopic total gastrectomy. According to the Lauren classification, diffuse type was present in 43 (46.74%) patients, intestinal type in 38 (41.3%) patients, and mixed type cancer in 11 (11.96%) patients. The tumor was located in the proximal third in 28 (30.43%) patients, in the central third in 26 (28.26%) patients, and in the distal third in 31 (33.7%) patients, while 7 (7.61%) patients had linitis plastica. According to TNM stage evaluation, 27 (29.35%) patients presented at stage 3A, 14 (15.22%) patients at stage 3B, 21 (22.83%) patients at stage 3C, and 2 (2.17%) patients at stage 4. During the follow-up period, recurrence was observed in 35 (38.04%) patients and 72 (78.26%) patients died. While mean hemoglobin values were 12.02±1.98 g/dL in GC patients, mean albumin levels were 4±0.57 g/dL. The median RDW values were 15.1 (13.95-16.9) %.

ROC analysis indicated that the optimal pre-operative RDW cut-off value for mortality prediction was 14.5 (AUC=0.690, p=0.010) in GC patients (**Table 2**, **Figure 1**). Therefore, GC patients were divided into two groups: high pre-operative RDW group (>14.5, n=58) and low pre-operative RDW (<14.5, n=34) (**Table 3**). Increased tumor size and decreased albumin and hemoglobin values were present in patients with high pre-operative RDW (p=0.036, 0.003, <0.001, respectively). The number of patients in the N0 stage was lower in the high pre-operative RDW group (p=0.013).

Table 2. Performance of the RDW to predict mortality

Cut-off	≥ 14.5
Sensitivity	72.22%
Specificity	70.00%
Accuracy	71.74%
PPV	89.66%
NPV	41.18%
AUC (95.0% CI)	0.690 (0.533-0.846)
p value	0.010

RDW: Red cell distribution width, PPV: Positive Predictive Value, NPV: Negative Predictive Value, AUC: Area Under ROC Curve, CI: Confidence Intervals

Table 1. The demographic features and tumor characteristics of patients

Age, years	63.85±14.06
Gender	
Female	32 (34.78%)
Male	60 (65.22%)
Time between diagnosis and operation, days	16 (9-26)
Surgical Procedure	
Subtotal	25 (27.17%)
Total	66 (71.74%)
Laparoscopic subtotal	0 (0.00%)
Laparoscopic total	1 (1.09%)
Differentiation	
Poor	55 (59.78%)
Moderate	24 (26.09%)
Well	13 (14.13%)
Histology	
Adenocarcinoma	60 (65.22%)
Signet ring cell adenocarcinoma	30 (32.61%)
Mucinous adenocarcinoma	2 (2.17%)
Lauren classification	
Intestinal	38 (41.30%)
Diffuse	43 (46.74%)
Mixed	11 (11.96%)
Location	
Proximal 1/3	28 (30.43%)
Central 1/3	26 (28.26%)
Distal 1/3	31 (33.70%)
Linitis plastica	7 (7.61%)
Tumor size, mm	50 (30-80)
Number of lymph nodes	20 (13-32)
Number of metastatic lymph nodes	4 (1-13.5)
Extracapsular invasion	39 (42.39%)
Lymph node dissection	
D1	18 (19.57%)
D2	47 (51.09%)
D1+	2 (2.17%)
D2+	25 (27.17%)
Perineural invasion	67 (72.83%)
Lymphovascular invasion	61 (66.30%)
Surgical margin positivity	12 (13.04%)
T stage	
T1	12 (13.04%)
T2	5 (5.43%)
T3	36 (39.13%)
T4	39 (42.39%)
N stage	
N0	21 (22.83%)
N1	16 (17.39%)
N2	24 (26.09%)
N3	31 (33.70%)
M stage	
M0	90 (97.83%)
M1	2 (2.17%)
TNM stage	
Stage 1A	9 (9.78%)
Stage 1B	3 (3.26%)
Stage 2A	8 (8.70%)
Stage 2B	8 (8.70%)
Stage 3A	27 (29.35%)
Stage 3B	14 (15.22%)
Stage 3C	21 (22.83%)
Stage 4	2 (2.17%)
Adjuvant chemotherapy	77 (83.70%)
Adjuvant radiotherapy	57 (61.96%)
Length of hospitalization, days	9 (6-12)
Leakage	16 (17.39%)
Infection	27 (29.35%)
Recurrence	35 (38.04%)
Albumin, g/dL	4.00±0.57
Hemoglobin, g/dL	12.02±1.98
RDW, %	15.10 (13.95-16.90)
Final Status	
Exitus	72 (78.26%)
Alive	20 (21.74%)

RDW: Red cell distribution width, Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage)

Table 3. Patient characteristics and clinicopathological features with regard to RDW level

	RDW		p
	< 14.5 (n=34)	≥ 14.5 (n=58)	
Age, years	61.21±15.39	65.40±13.11	0.169
Gender			0.882
Female	11 (32.35%)	21 (36.21%)	
Male	23 (67.65%)	37 (63.79%)	
Surgical Procedure			0.733
Subtotal	9 (26.47%)	16 (27.59%)	
Total	25 (73.53%)	41 (70.69%)	
Laparoscopic subtotal	0 (0.00%)	0 (0.00%)	
Laparoscopic total	0 (0.00%)	1 (1.72%)	
Differentiation			0.735
Poor	20 (58.82%)	35 (60.34%)	
Moderate	8 (23.53%)	16 (27.59%)	
Well	6 (17.65%)	7 (12.07%)	
Histology			0.454
Adenocarcinoma	24 (70.59%)	36 (62.07%)	
Signet ring cell adenocarcinoma	10 (29.41%)	20 (34.48%)	
Mucinous adenocarcinoma	0 (0.00%)	2 (3.45%)	
Lauren classification			0.626
Intestinal	12 (35.29%)	26 (44.83%)	
Diffuse	17 (50.00%)	26 (44.83%)	
Mixed	5 (14.71%)	6 (10.34%)	
Location			0.287
Proximal 1/3	13 (38.24%)	15 (25.86%)	
Central 1/3	11 (32.35%)	15 (25.86%)	
Distal 1/3	9 (26.47%)	22 (37.93%)	
Linitis plastica	1 (2.94%)	6 (10.34%)	
Tumor size, mm	35 (27±75)	60 (40±80)	0.036
Number of lymph nodes	21 (15±29)	19 (13±34)	0.971
Number of metastatic lymph nodes	2.5 (0±11)	4.5 (2±17)	0.102
Extracapsular invasion	12 (35.29%)	27 (46.55%)	0.403
Lymph node dissection			0.240
D1	7 (20.59%)	11 (18.97%)	
D2	21 (61.76%)	26 (44.83%)	
D1+	0 (0.00%)	2 (3.45%)	
D2+	6 (17.65%)	19 (32.76%)	
Perineural invasion	22 (64.71%)	45 (77.59%)	0.272
Lymphovascular invasion	20 (58.82%)	41 (70.69%)	0.350
Surgical margin positivity	4 (11.76%)	8 (13.79%)	1.000
T stage			0.688
T1	5 (14.71%)	7 (12.07%)	
T2	3 (8.82%)	2 (3.45%)	
T3	12 (35.29%)	24 (41.38%)	
T4	14 (41.18%)	25 (43.10%)	
N stage			0.013
N0	14 (41.18%)	7 (12.07%)	
N1	4 (11.76%)	12 (20.69%)	
N2	6 (17.65%)	18 (31.03%)	
N3	10 (29.41%)	21 (36.21%)	
M stage			0.529
M0	34 (100.00%)	56 (96.55%)	
M1	0 (0.00%)	2 (3.45%)	
TNM stage			0.069
Stage 1A	5 (14.71%)	4 (6.90%)	
Stage 1B	2 (5.88%)	1 (1.72%)	
Stage 2A	6 (17.65%)	2 (3.45%)	
Stage 2B	2 (5.88%)	6 (10.34%)	
Stage 3A	8 (23.53%)	19 (32.76%)	
Stage 3B	2 (5.88%)	12 (20.69%)	
Stage 3C	9 (26.47%)	12 (20.69%)	
Stage 4	0 (0.00%)	2 (3.45%)	
Adjuvant chemotherapy	30 (88.24%)	47 (81.03%)	0.542
Adjuvant radiotherapy	21 (61.76%)	36 (62.07%)	1.000
Length hospitalization, days	9 (7±11)	10 (6±13)	0.630
Leakage	3 (8.82%)	13 (22.41%)	0.169
Infection	8 (23.53%)	19 (32.76%)	0.483
Recurrence	12 (35.29%)	23 (39.66%)	0.847
Albumin, g/dL	4.22±0.43	3.86±0.60	0.003
Hemoglobin, g/dL	13.16±1.69	11.35±1.83	<0.001
Final Status			0.001
Exitus	20 (58.82%)	52 (89.66%)	
Alive	14 (41.18%)	6 (10.34%)	

RDW: Red cell distribution width. Data are given as mean±standard deviation or median (1st quartile±3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage)

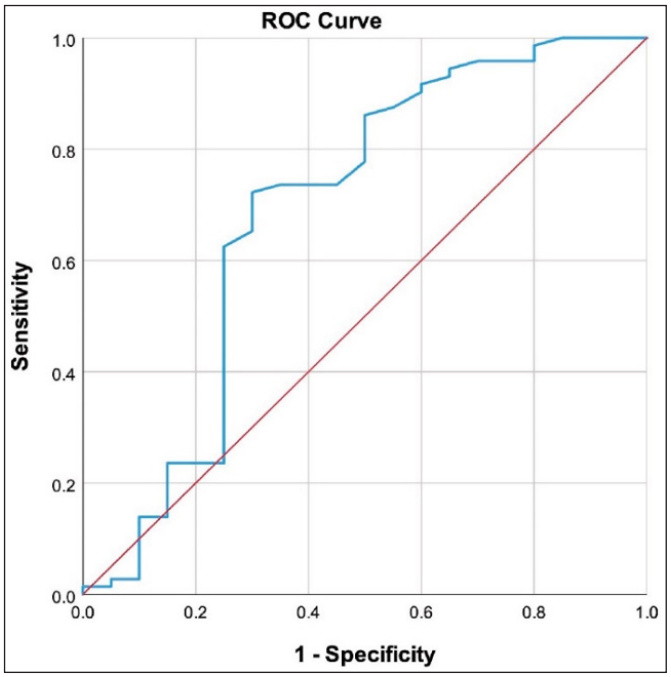

Figure 1. ROC curve of the RDW to predict mortality

Five-year OS rates were examined with Kaplan-Meier method and comparisons were performed with the Log rank test (**Table 4**). Overall, 5-year OS was 27.2±4.8 %. Intestinal type GC showed significantly higher OS rates than diffuse type GC (p=0.020). Patients with linitis plastica demonstrated significantly lower OS rate compared to other locations (p=0.006). Lower OS rates were observed in GC patients with extracapsular invasion, perineural invasion, lymphovascular invasion, leakage, infection, and recurrence, as well as in those with surgical margin positivity and higher RDW values (all, p<0.05). T4 and also N3 stage showed decreased OS rates than the other stages (all, p=<0.001). Lower OS rates were found in stage 3&4 compared to stage 1 and 2 (p=<0.001). The OS rates were 17.6±5% in patients with high-RDW and 44.5±9% in the low-RDW group (p=<0.001).

We performed Cox regression analysis to determine the best prognostic factors associated with mortality (**Table 5**). We found perineural invasion, surgical margin positivity, N3 stage, leakage and high RDW as poor prognostic factors. Patients with perineural invasion had 2.395-fold higher risk of death than those without (HR: 2.395, 95% CI: 1.268-4.526, p=0.007) (**Figure 2**). Patients with positive surgical margin presented 2.220-fold higher risk of death than those without (HR: 2.220, 95% CI: 1.040-4.740, p=0.039) (**Figure 3**). Patients with N3 stage tumor showed 3.223-fold higher risk of death than those without (HR: 3.223, 95% CI: 1.763-5.893, p<0.001) (**Figure 4**). Patients with leakage demonstrated 5.112-fold higher risk of death compared to those without leakage (HR: 5.112, 95% CI: 2.679-9.755, p<0.001) (**Figure 5**). Patients

with high RDW (≥ 14.5) had 1.978-fold higher risk of death than patients classified in the low RDW group (HR: 1.978, 95% CI: 1.166-3.357, p=0.011) (**Figure 6**). Other variables included in the model were non-significant, including Lauren classification (p=0.364), location (p=0.577), extracapsular invasion (p=0.991), lymphovascular invasion (p=0.106), T stage (p=0.165), TNM stage (p=0.293), infection (p=0.079), recurrence (p=0.547), time between diagnosis and surgery (p=0.229), tumor size (p=0.248), total number of lymph nodes (p=0.613), number of metastatic lymph nodes (p=0.500), albumin (p=0.182) and hemoglobin (p=0.803).

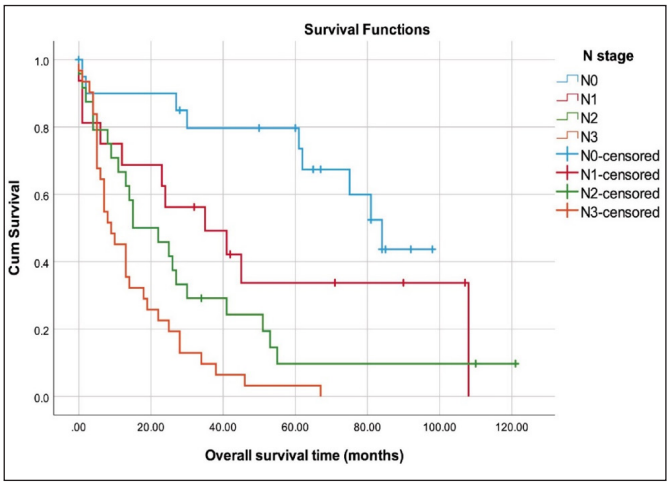

Figure 4. Overall survival plot with regard to N stage

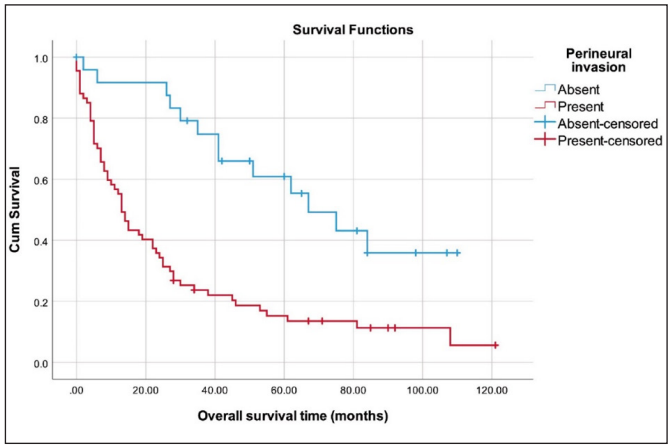

Figure 2. Overall survival plot with regard to perineural invasion

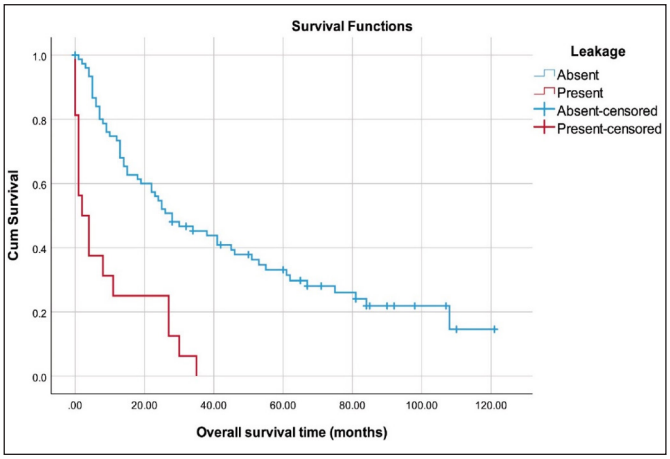

Figure 5. Overall survival plot with regard to leakage

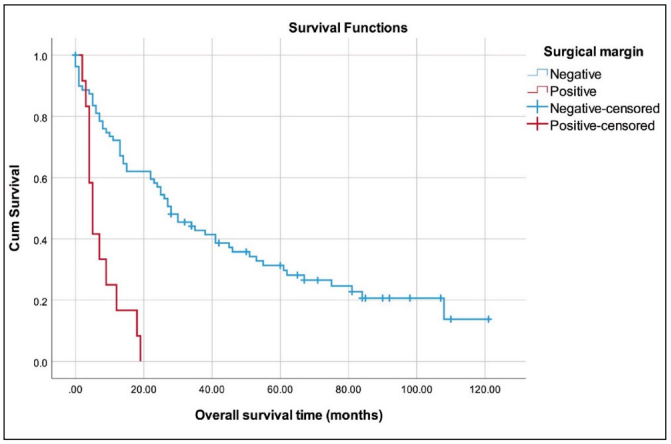

Figure 3. Overall survival plot with regard to surgical margin positivity

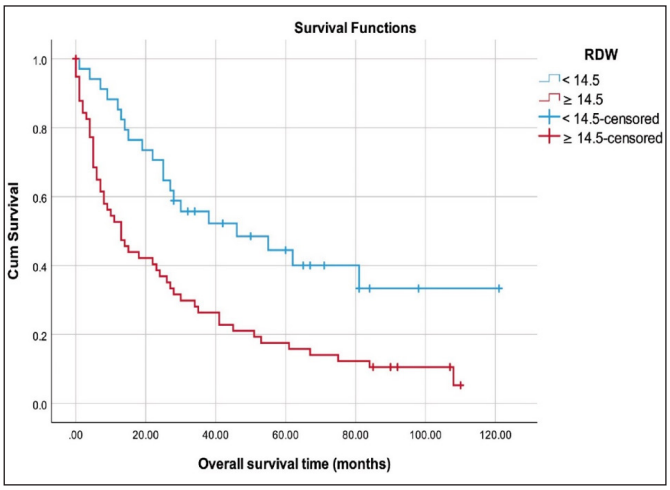

Figure 6. Overall survival plot with regard to RDW level

Table 5. Significant prognostic factors of the mortality, Cox regression analysis

	β Coefficient	Std Error	p	Exp(β)	95.0% CI for Exp(β)	
Perineural invasion	0.873	0.325	0.007	2.395	1.268	4.526
Surgical margin positivity	0.798	0.387	0.039	2.220	1.040	4.740
N3 stage	1.170	0.308	<0.001	3.223	1.763	5.893
Leakage	1.632	0.330	<0.001	5.112	2.679	9.755
RDW (≥ 14.5%)	0.682	0.270	0.011	1.978	1.166	3.357

CI: Confidence interval, RDW: Red cell distribution width

Table 4. Survival times (months) with Kaplan Meier method and comparisons of groups with Log rank test

	n	Exitus	Mean (95.0% CI)	Median (95.0% CI)	5-years survival rate (%)	p
Overall survival	92	72	40.11 (31.32±48.90)	24 (13.81±34.19)	27.2±4.8	N/A
Age						0.214
< 65 years	46	34	45.59 (32.60±58.59)	26 (19.35±32.65)	32.0±7.0	
≥ 65 years	46	38	33.84 (23.04±44.64)	15 (7.12±22.88)	22.8±6.5	
Gender						0.367
Female	32	26	32.00 (20.65±43.34)	18 (4.92±31.08)	24.7±7.9	
Male	60	46	43.04 (31.75±54.32)	25 (16.33±33.68)	28.5±6.0	
Surgical Procedure						0.087
Subtotal	25	17	51.05 (34.37±67.73)	41 (9.95±72.05)	41.7±10.1	
Total	67	55	35.11 (25.45±44.78)	19 (8.69±29.31)	21.6±5.3	
Differentiation						0.175
Poor	55	46	34.56 (24.29±44.84)	19 (7.70±30.31)	20.8±5.7	
Moderate	24	18	38.47 (21.57±55.37)	15 (0.00±30.36)	26.8±9.5	
Well	13	8	54.17 (35.69±72.64)	62 (11.14±112.86)	52.7±14.1	
Histology						0.145
Adenocarcinoma	60	45	40.91 (31.08±50.74)	27 (21.42±32.58)	28.8±6.1	
Signet ring cell adenocarcinoma	30	25	31.25 (16.50±46.00)	9 (1.49±16.52)	18.8±7.3	
Lauren classification						0.020
Intestinal	38	25	52.49 (38.62±66.35)[a]	41 (6.33±75.67)	45.2±8.3	
Diffuse	43	38	27.82 (17.49±38.15)[b]	14 (5.01±22.99)	11.5±5.2	
Mixed	11	9	39.55 (12.97±66.12)[ab]	19 (3.90±34.11)	24.2±13.8	
Location						0.006
Proximal 1/3	28	24	29.44 (15.78±43.10)[a]	22 (11.63±32.37)	10.9±6.6	
Central 1/3	26	19	46.79 (30.35±63.23)[a]	27 (3.79±50.21)	37.3±9.7	
Distal 1/3	31	22	48.17 (32.93±63.41)[a]	41 (8.91±73.09)	39.1±9.0	
Linitis plastica	7	7	9.71 (5.85±13.58)[b]	11 (0.00±26.40)	0.0±0.0	
Extracapsular invasion						<0.001
Absent	53	35	53.22 (41.64±64.80)	51 (26.38±75.62)	44.1±7.1	
Present	39	37	19.64 (11.42±27.86)	12 (7.11±16.89)	5.1±3.5	
Lymph node dissection						0.112
D1 & D1+	20	14	51.54 (33.72±69.36)	35 (10.90±59.11)	39.4±11.1	
D2	47	35	40.84 (27.75±53.93)	22 (9.67±34.33)	29.0±6.9	
D2+	25	23	28.54 (15.64±41.45)	18 (3.31±32.69)	14.4±7.3	
Perineural invasion						<0.001
Absent	25	13	69.19 (53.85±84.53)	67 (43.88±90.12)	60.9±10.3	
Present	67	59	28.51 (19.89±37.14)	13 (9.99±16.01)	15.2±4.5	
Lymphovascular invasion						<0.001
Absent	31	16	68.12 (52.75±83.48)	81 (40.09±121.91)	58.2±9.3	
Present	61	56	25.22 (17.28±33.16)	13 (9.72±16.28)	12.3±4.3	
Surgical magrin						<0.001
Negative	80	60	45.04 (35.39±54.7)	28 (19.40±36.60)	31.3±5.4	
Positive	12	12	7.67 (4.41±10.92)	5 (3.33±6.67)	0.0±0.0	
T stage						<0.001
T1 & T2	17	9	65.08 (49.01±81.16)[a]	75 (43.65±106.35)	61.9±12.3	
T3	36	28	44.54 (30.52±58.57)[a]	27 (19.76±34.24)	31.2±8.1	
T4	39	35	21.06 (12.46±29.67)[b]	12 (5.88±18.12)	9.0±4.8	
N stage						<0.001
N0	21	9	72.49 (58.08±86.90)[a]	84 (69.59±98.41)	79.7±9.1	
N1	16	11	49.78 (26.50±73.06)[ab]	35 (4.93±65.07)	33.8±12.6	
N2	24	21	30.90 (17.02±44.79)[b]	15 (1.80±28.20)	9.7±6.4	
N3	31	31	15.13 (9.84±20.42)[c]	9 (4.76±13.24)	3.2±3.2	
TNM stage						<0.001
Stage 1	12	5	77.42 (62.70±92.14)[a]	84 (62.79±105.21)	81.8±11.6	
Stage 2	16	10	60.46 (38.64±82.28)[a]	61 (22.11±99.89)	53.7±13.0	
Stage 3 & 4	64	57	26.39 (18.00±34.78)[b]	13 (9.52±16.48)	10.9±4.1	
Adjuvant chemotherapy						0.202
Absent	15	13	27.68 (12.53±42.84)	10 (0.00±27.99)	25.0±11.6	
Present	77	59	42.24 (32.43±52.06)	25 (16.46±33.54)	27.8±5.3	
Adjuvant radiotherapy						0.502
Absent	35	26	41.46 (29.05±53.86)	30 (16.15±43.86)	37.1±8.5	
Present	57	46	37.48 (26.54±48.42)	19 (8.43±29.57)	21.3±5.6	
Leakage						<0.001
Absent	76	56	46.70 (36.72±56.69)	28 (14.15±41.85)	33.1±5.6	
Present	16	16	9.50 (3.35±15.65)	2 (0.00±5.92)	0.0±0.0	
Infection						0.001
Absent	65	47	48.01 (37.27±58.76)	30 (15.07±44.93)	33.9±6.1	
Present	27	25	19.32 (8.84±29.79)	10 (0.00±20.18)	11.1±6.0	
Recurrence						0.011
Absent	57	38	50.24 (37.18±63.31)	30 (0.00±77.83)	43.9±6.7	
Present	35	34	24.40 (18.53±30.27)	22 (15.05±28.95)	2.9±2.8	
RDW						0.001
<14.5%	34	20	61.21 (44.65±77.77)	46 (7.54±84.46)	44.5±9.0	
≥14.5%	58	52	28.57 (19.76±37.38)	13 (6.67±19.33)	17.6±5.0	

CI: Confidence interval, RDW: Red cell distribution width

DISCUSSION

This study aimed to reveal the associations between pre-operative RDW values and clinicopathological features of GC and to evaluate its predictive impact on progression and prognosis of GC. We found that pre-operative RDW was associated with tumor size, N stage, and pre-operative albumin and hemoglobin values in patients with GC. The cut-off value for pre-operative RDW (>14.5) could be used to predict mortality in GC patients. We also demonstrated that perineural invasion, surgical margin positivity, N3 stage, leakage and high RDW value may be used as independent prognostic indicators for OS in GC patients.

Recent studies have drawn attention to the link between inflammation and malignancies, and have shown that cancer can act as a cause or consequence of chronic inflammation. Additionally, cancer-related inflammation plays a substantial role in tumor pathogenesis, including GC, which involves initiation, progression, metastasis and clinical prognosis (10). Chronic inflammation may cause poor response to chemotherapy, resulting in a worse prognosis for cancer patients (11). Possible links may also exist with aberrant triggering of multiple signaling pathways, including angiogenesis, abnormal apoptosis, increased cytokine production, inappropriate immune cell proliferation/differentiation, epithelial transformation, and nutritional factors (10). Although clinicopathological factors of GC, such as TNM stage, lymph node metastases and lymphatic vessel invasion, are utilized to aid patient risk classification and treatment approaches, the complexity of the pathogenesis of GC prompts researchers to investigate more suitable indicators in order to assess patients' clinical status for prognostic and therapeutic purposes (12).

RDW is a biomarker routinely analyzed in clinical laboratories to demonstrate heterogeneity in the size of circulating erythrocytes, and may reflect nutritional insufficiencies (folate, vitamin B12 or iron deficiency) which are often detected in GC patients, and can lead to significant decline in the emotional and physical status of GC patients (13). Recent studies have shown that increased RDW is related with oxidative stress and inflammation, and correlates with overall and disease-specific survival in diseases with progressive features or chronic inflammation (12, 14). In addition, RDW has received increasing attention in recent years in terms of malignancy pathogenesis and it has been found that elevated RDW value is related with diagnosis and survival in many cancer types, including esophageal, colorectal, pulmonary, hepatocellular, prostate, and breast cancers (15). Zhou et al. (6) reported in a meta-analysis of 13 studies involving 3509 patients with gastrointestinal cancer that patients with elevated RDW tended to have shorter OS and cancer-free survival compared to patients with low RDW. They also demonstrated that increased RDW was related with larger tumor size, deeper invasion, worse differentiation, more advanced clinical stage and earlier lymph node metastasis. Increased pre-operative RDW reported in cancer patients may be due to elevated inflammatory mechanisms induced by tumor cells and their microenvironment (16). High levels of secreted pro-inflammatory cytokines, such as IL-6, TNF-α and CRP, can inhibit erythropoietic activity on bone marrow erythrocyte stem cells and impair iron metabolism and homeostasis, and also shorten red blood cell survival, resulting in the release of more immature red blood cells into peripheral blood circulation and elevation of pre-operative RDW (17). It is also thought that RDW regulates cancer progression by inducing the glycolytic process of tumor cells, and that elevated RDW may be a surrogate indicator of advanced glucose metabolism, which is significant for the survival of GC patients (18). RDW is also related with impaired nutritional status, which has been reported to be associated with a lower response to management, worse prognosis, and quality of life in cancer patients (19).

Taking these relationships into account, we aimed to look over the prognostic value of RDW in GC patients. We found a significant cut-off value for pre-operative RDW that could identify mortality in GC patients (>14.5). Consistent with our results, Sakin et al. (20) demonstrated an RDW threshold of 14.1, with 61.3% sensitivity and 64% specificity in predicting the presence of GC in a large study including 330 GC patients and 330 healthy controls. Shota et al. (21) reported in 221 GC patients who underwent curative surgery that the optimal cut-off value for RDW was 14.85 pre-operatively and 14.05 post-operatively. Our result indicates that pre-operative RDW could be used as an indicator for predicting mortality in patients with GC. We then divided GC patients into two groups according to the cut-off value for RDW. We found that pre-operative RDW was associated with tumor size, lymph node stage as well as pre-operative albumin and hemoglobin. Similarly, Hirahara et al. (22) demonstrated a positive relationship between RDW and tumor size, lymph node metastasis, pathological stage, serum albumin and CRP levels in 366 GC patients. Yazici and colleagues (23) revealed that RDW is correlated with preoperative hemoglobin, tumor stage, tumor diameter and metastatic lymph nodes. Yuksel et al. (14) showed in 411 operated GC patients that elevated pre-operative RDW was present in patients with advanced TNM stage, advanced T stage, node positivity, hypoalbuminemia, more metastatic lymph nodes and increased age. Cheng et al. (12) reported that a higher RDW was related with

advanced age, deeper tumor infiltration, larger tumor size and lymph node metastasis. Our results suggest that RDW is involved in GC pathogenesis and tumor progression. We support the idea that increased RDW reflects tumor-associated systemic inflammation and impaired nutritional status.

In the present study, we found that high preoperative RDW, presence of extracapsular invasion, perineural invasion, lymphovascular invasion, leakage, infection and recurrence, T4 or N3 stage, linitis plastica, intestinal type GC, and surgical margin positivity were associated with worse OS in patients with GC. The OS rates were 17.6±5% in high-RDW patients and 44.5±9% in the low-RDW group. Similar to our result, Sakin et al. (20) found the 5-year OS rate was 57.7% in GC patients with high RDW and 74.4% low-RDW group, with an RDW value of >15.5 associated with 5.7-fold greater risk for recurrence. Shota et al. (21) demonstrated that 5 years OS rates differed significantly in the GC group with high RDW (>14.85 for RDW) (52.4%) compared to the low-RDW group (<14.85) (78%). In addition, after adjusting for other confounding factors, we performed Cox regression analysis to determine prognostic variables associated with mortality. We demonstrated that a high RDW value, perineural invasion, surgical margin positivity, N3 stage, and the presence of leakage were independent prognostic factors for mortality in GC patients who underwent surgical resection. These factors were significantly associated with postoperative mortality and disease prognosis. This was consistent with the literature (12, 20, 21). Our results indicate that RDW was a powerful prognostic factor that could be used to classify patients with high mortality risk.

Several limitations should be acknowledged. First, our study was a retrospective, single-center study including few patients, which may have led to various types of bias. Secondly, we could not identify those who died from non-GC causes due to long follow-up and data loss, leading to lack of disease-specific analyses.

CONCLUSION

Our results indicate that RDW is associated with GC pathogenesis and tumor progression. The pre-operative RDW cut-off value of 14.5 could be used to predict mortality in GC patients. A high RDW value, perineural invasion, surgical margin positivity, N3 stage, and the presence of leakage may be used as independent prognostic indicators of OS in GC patients. The fact that RDW measurement is non-invasive, easily accessible and fast will provide convenience to physicians in predicting GC patients at high risk for mortality..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 15.06.2021, Decision No: 03).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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